Government of Canada / Gouvernement du Canada

Practical Approaches to Develop Case Studies: Perspectives from Accelerating the Pace of Chemical Risk Assessment (APCRA)

RAD/CHEM AOP Workshop
Adverse Outcome Pathway Integration into Radiation Risk Assessment
October 7-8, 2020

Tara Barton-Maclaren, *PhD, Research Manager, Existing Substances Risk Assessment, HC*

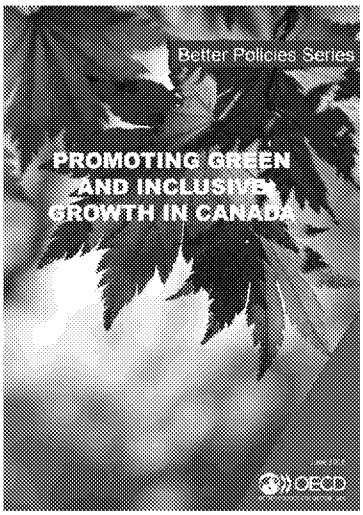
Canada

Global Challenges for Chemicals Management

- Aggressive priority setting and assessment mandates
- Rapidly changing chemical landscape
  - Continual stream of new and more complex chemistries
  - Focus on issues including complex mixtures, cumulative risk
- Majority of commercial chemicals are 'data poor" and standard toxicity testing protocols are resource intensive
- Pressure to reduce/eliminate animal testing
  - e.g., EU cosmetics regulations; Lautenberg Act in US; EPA Administrator Directive (Sept 2019); Ban for cosmetics in Australia (July 2020); Private Member's Bill S-214
- Need for broader data availability
  - CBI Issues
- Performance Measurement – are we making a difference?

OECD Report: Ensuring a Sustainable Chemicals Management Programme beyond 2020

- "While Canada was one of the first countries to systematically start addressing the risks of legacy chemicals, the priority-setting exercise is now almost a decade old. **It is essential for Canada to take into consideration new scientific information regarding chemicals and to support the continued development of modernised and harmonised approaches for the assessment and management, of chemicals,** ensuring a sustainable chemicals management programme beyond the 2020 goal."



Promoting Green and Inclusive Growth in Canada; Better Policies Series, OECD 2016

NAM: New Approach Methodologies

Ambition: define how New Approach Methodologies can be used in a regulatory context to enhance the pace of our work, to have better informed, more relevant decisions and reduce/replace the need for studies on (vertebrate) animals, with a main focus on high tier human health and environmental 'endpoints'.

What is a "New Approach Methodology"?

- As a working definition: a method that (potentially) can significantly contribute to fulfil this ambition in terms of:
  - Throughput and/or
  - Robustness and/or;
  - Bringing mechanistic knowledge and/or;
  - Providing appropriate protection levels for human health and Environment.

We are exploring the use of NAM in priority setting, enhancing read-across, integrated into WoE/IATA/DA [1], and as a 'stand alone' assessment tool.

1: WoE: Weight of Evidence: https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/weight-of-evidence
IATA: Integrated Approaches to Testing and Assessment: http://www.oecd.org/chemicalsafety/risk-assessment/iata-integrated-approaches-to-testing-and-assessment.htm
DA: Defined Approach http://www.oecd.org/publications/guidance-document-on-the-reporting-of-defined-approaches-to-be-used-within-integrated-approaches-to-testing-and-assessment-9789264274822-en.htm

Technical Capacity Building:

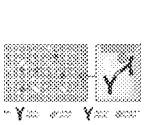
Healthy Environments and Consumer Safety Branch

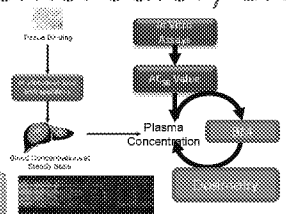
Health Canada

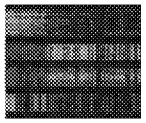
CANADIAN CENTRE FOR ALTERNATIVES TO ANIMAL METHODS

CANADIAN CENTRE FOR THE VALIDATION OF ALTERNATIVE METHODS

University of Windsor







Indoor and Outdoor Air

Products and Consumables

Research

Drinking Water

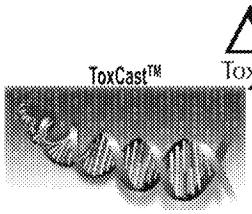
Drinking Substances

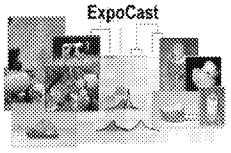
Food Substances

McGill

CIHR IRSC

RISK21





Accelerating the Pace of Chemical Risk Assessment

APCRA

OECD BETTER POLICIES FOR BETTER LIVES

ECHA EUROPEAN CHEMICALS AGENCY

Technical Capacity Building: Benefits of Regulatory Cooperation:

- Ongoing engagement and established processes strengthen and contribute to the work of international technical experts.
- This enables the advancement of work and acceptance of approaches in areas such as NAMs by addressing barriers with pragmatic solutions to transform chemical risk assessment

Accelerating the Pace of Chemical Risk Assessment
APCRA

ECHA
EUROPEAN CHEMICALS AGENCY

Health Canada

- Workshops bring regulators together to discuss progress and barriers for applying new tools to prioritization and risk assessment
- Collaborations with international regulators on case studies to facilitate acceptance for the implementation of emerging technologies
- Risk-based screening and assessment approaches being examined for both human and ecological receptors

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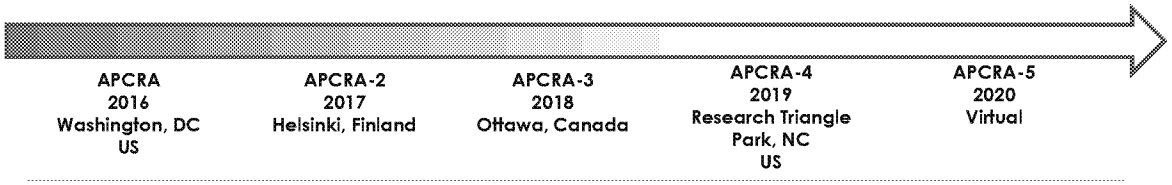
NAMs are emerging tests and approaches that can be used to further inform chemical hazard characterization and risk assessment and broadly include in chemico assays, in vitro assays and in silico methods

Case Studies
Using NAMS to address data poor, high exposure chemicals
Use NAMS to improve chemical categories and biological activity groupings
In vitro bioactivity as a conservative PoD
New tools to predict exposures from various chemical structure and use categories
Develop multimedia exposure models to improve lead mitigation efforts
Develop an inventory of validated NAMS to identify endocrine disruptors
Application of NAMS to perfluoroalkylated substances
Develop reference doses from endocrine disruptors from in vitro assays

What is APCRA?

- A series of international workshops that bring together governmental entities engaged in development of higher throughput hazard, exposure, and risk assessment methods and approaches in their chemical evaluation activities.
  - To discuss progress and barriers in applying new tools to prioritization, screening, and quantitative risk assessment of differing levels of complexity.
  - To discuss opportunities to increase collaboration in order to accelerate the pace of chemical risk assessment.



APCRA	APCRA-2	APCRA-3	APCRA-4	APCRA-5
2016	2017	2018	2019	2020
Washington, DC US	Helsinki, Finland	Ottawa, Canada	Research Triangle Park, NC US	Virtual

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What are the current barriers to acceptance for successful use of NAMs in regulatory decision-making?

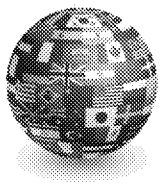
What are near-term efforts that can improve use of NAM data?

What is needed to lead to acceptance of NAMs by regulators and the public?

Participants

~100 participants ~20-25+ new

- A*STAR Singapore
- Amthem Blue Cross
- Australian Industrial Chemicals Introduction Scheme
- Cal-EPA
- Defra UK
- ECHA
- EFSA
- Environment and Climate Change Canada
- Health Canada
- INERIS (French national institute for industrial environment and risks)
- Kaviock Consulting LLC
- Ministry of the Environment, Japan
- National Research Council of Canada
- NIEHS
- OECD
- U.S. Consumer Product Safety Commission
- University Hospital Cologne
- University of Birmingham
- US EPA
- US FDA
- Others …



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SAHTECH- Safety and Health Technology Center, Taiwan
A*STAR – Agency for Science, Technology and Research, Singapour
NITE – National Institute of Technology and Evaluation

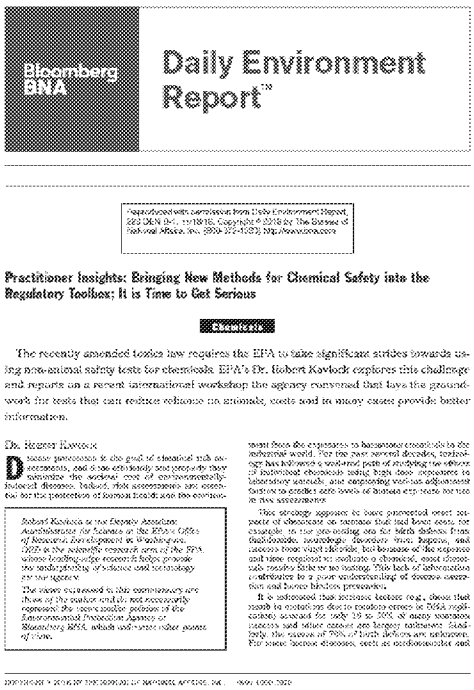
APCRA Goals

- Common understanding of current state of the science applications of New Approach Methods (NAMs), including the regulatory context.
- Increased understanding of realistic benchmarks for performance of NAMs in different regulatory contexts.
- Determine mechanisms to enhance data sharing capabilities.
- Increase engagement and commitment to development and sharing of case studies of mutual interest.
- Increased cross-Agency collaboration to strategically address barriers and limitations of use of NAMs in a regulatory context.

Goals and Outcomes of First Workshop

- **Washington, DC (2016)**
- **Focus of the first workshop**
  - Compilation of a master list of chemicals of common international interest for ongoing and future NAM application
  - Identification of potential sources of NAM information and how such information could be shared and exploited
  - Common understanding of current state of the science applications of New Approach Methods (NAMs), including the regulatory context and presentation of practical examples
  - Commitment to development and sharing of case studies of mutual interest

- **A total of 10 case studies were originally proposed**



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Practitioner Insights: Bringing New Methods for Chemical Safety into the Regulatory Toolbox; It is Time to Get Serious

Abstract

The recently amended toxics law requires the EPA to take significant strides towards using non-animal safety tests for chemicals. EPA's Dr. Robert Kavlock explores this challenge and reports on a recent international workshop the agency convened that lays the groundwork for tests that can evidence reliance on animals, could lead to many cases provide better information.

Dr. Robert Kavlock

Robert Kavlock is the Deputy Associate Administrator for Science in the Office Office of Research Development in Washington. ORD is the scientific research arm of the EPA whose leading-edge research helps provide the underpinning of science and technology for the agency.

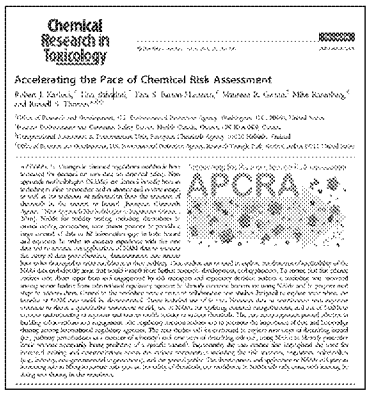
The views expressed in this commentary are those of the author and do not necessarily represent the views and/or policies of the Environmental Protection Agency or Bloomberg BNA, which welcomes other points of view.

https://news.bloombergenvironment.com/environment-and-energy/practitioner-insights-bringing-new-methods-for-chemical-safety-into-the-regulatory-toolbox-it-is-time-to-get-serious-2

A total of 10 case studies were originally proposed

Goals and Outcomes of Second Workshop

- **Helsinki (2017)**
- **Focus of the second workshop**
  - Identifying and addressing critical data gaps
  - Understanding requirements for acceptance of NAMs by regulators and the public
  - Adding NAMs for exposure analysis
- **A total of 6 case studies were continued**



https://pubs.acs.org/doi/10.1021/acs.chemrestox.7b00339

A total of 6 case studies were continued

Goals and Outcomes of Third Workshop

- **Hosted by Health Canada**
- **Ottawa, ONTARIO (2018)**

- **Focus of the third workshop**
  - Identifying and addressing critical data gaps
  - Increasing understanding of realistic benchmarks for performance of NAMs in different regulatory contexts.
  - Adding NAMs for ecotoxicology analysis

- **A total of 4 new case studies were proposed**

 https://news.bloombergenvironment.com/environment-and-energy/insight-new-approaches-to-chemical-assessment-a-progress-report

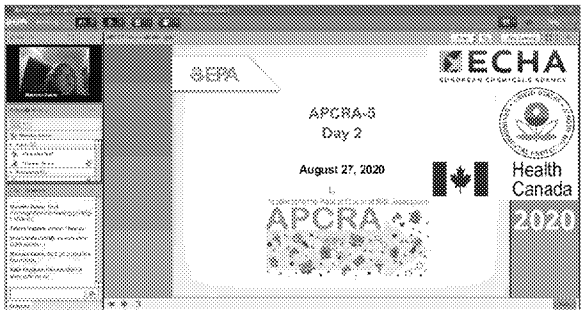
Goals and Outcomes of Fourth Workshop

- **Hosted by US EPA**
- **Research Triangle Park, NC (2019)**
- **Focus of the fourth workshop**
  - Overview of current and new case studies
  - Progress in applying new approach methodologies (NAMs) in different regulatory contexts
  - Integration of NAMs in risk assessment
- **A total of 4 new case studies were proposed**
- **APCRA-4 Public Update**
  - Webinar designed to share updates from the October meeting, March 2020

13 https://chemicalwatch.com/123913/expert-focus-advancing-new-approach-methodologies-for-chemical-risk-assessment

Goals and Outcomes of Fifth Workshop

- **Hosted Virtually**
- **Focus of the fifth workshop**
- Increased engagement and commitment to development and sharing of case studies of mutual interest.
- Increased cross-Agency collaboration to strategically address barriers and limitations of use of NAMs in a regulatory context.
- Increased understanding of current and proposed APCRA case studies and what data gaps remain to be addressed.
- **A total of 4 new case studies were proposed**



Communication – Publications & Resources

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Accelerating the Pace of Chemical Risk Assessment (APCRA)

The advent of New Approach Methods (NAMs) for generating exposure and hazard information on chemicals provides an opportune time to explore advances in risk science to support the global transition toward 21st century approaches to chemical risk assessment. Accelerating the Pace of Chemical Risk Assessment (APCRA) is an international government-to-government initiative whose aim is to promote collaboration and dialogue on the scientific and regulatory needs for the application and acceptance of NAMs in regulatory decision making.

In 2016, EPA hosted the first APCRA workshop to discuss the development and application of NAMs for chemical risk assessment with international regulators. Case studies were initiated following this first workshop; these as well as new case study proposals introduced on an ongoing basis continue to be discussed at subsequent annual workshops which to date have been hosted by the European Chemicals Agency (ECHA), Health Canada and EPA. The APCRA initiative has focused on how to modernize quantitative risk assessment and demonstrate how the data and tools can be incorporated into future risk assessment activities, in particular for chemicals with limited information.

The purpose of these meetings has been for sharing data, knowledge, experience, and expertise among international government entities that are considering or currently applying emerging science in regulatory decisions including priority setting, hazard identification and/or risk assessment for the large number of chemicals in commerce or that are being proposed for introduction to the market internationally. Participants include governmental entities from North America, Europe and Australasia. Efforts to date have led to collaborative case studies on the use of alternative methods in regulatory contexts.

Important Links

- First Workshop Summary
- Second Workshop Summary
- Third Workshop Summary
- APCRA Joint Case Study: Utility of In Vitro Bioactivity as a Lower Bound Estimate of In Vivo Adverse Effect Levels and in Risk-Based Prioritization

Publications and Resources

- Publications
- APCRA Case Studies

https://www.epa.gov/chemical-research/accelerating-pace-chemical-risk-assessment-apcra

APCRA Activities

General Requirements for the APCRA Case Studies:

- must fit the criteria of promoting collaboration and dialogue on the scientific and regulatory needs for the application and acceptance of NAMs in clear regulatory context;
- include international collaborative case studies on topics of interest to multiple regulatory agencies;
- have largely been communicated through presentations at professional meetings and publications.

APCRA Case Studies

- **Application to Risk Evaluation**
  - Bioactivity as a conservative estimate of PODs
  - Quantitative and qualitative comparison of NAMs and traditional animal toxicity testing for data poor chemicals
  - Use of transcription profiles and primary human liver cells grown as spheroids to address potency and additivity of perfluorinated alkylated substances.
- **Application to Chemical Categorization**
  - Develop NAM profiles based on available data (e.g., highthroughput in vitro assay data) for existing chemical categories
  - Evaluate the effectiveness of EcoNAMs, specifically omics technologies used in conjunction with third-wave machine learning, to derive molecular data for mechanism-driven substance grouping..
- **Application to Exposure Evaluation**
  - Use of innovative modeling and GIS approaches by various agencies for assessing lead exposures
  - Triaging chemical exposure data needs and tools for next-generation risk assessment

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Workflows for NAMs implementation:
Development of tiered frameworks or workflows to leverage NAMs for data poor substances
Identification of NAM to address data gaps

Role of Bioactivity and Exposure:
Bioactivity (AED) as POD – in vitro assay data, transcriptomics (protective approach)
BER as risk-based approach for prioritization and assessment – human health and ecological
HTTK

Chemical Categorization:
Harnessing of NAM data and tools for chemical categories and read-across
Use of data for identifying biological responses, pathways (AOPs), mode of action, potency comparison

Key substances or biological endpoints:
Genetic toxicity
Endocrine disruption
Repeat-dose toxicity
Per/poly-fluoroalkyl substances
Nanofibers

Data Analysis/Integration Mechanisms:
Machine learning approaches
Data mining workflows and monitoring emerging data
Systematic review – evidence mapping, systematic review extraction and evaluation

Proposing New Case Studies

APCRA New Case Study Proposal template

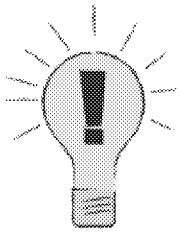
1. Title of Case Study:
2. Lead organization:

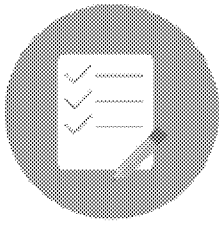
Case Study Point of Contact:	
Contact Information (email, phone):	
Organization:	

3. Potential Collaborator(s):

Case Study Point of Contact:	
Contact Information (email, phone):	
Organization:	

4. Problem to be addressed by case study:
5. Aim/Purpose of case study:
6. Main Steps/General Timeframe:
7. Expected Regulatory Application/Impact of Case Study:

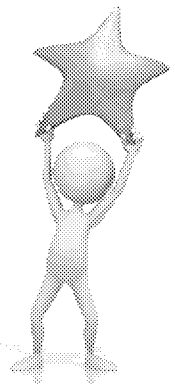




- ❑ Regulatory need & application
- ❑ Increase acceptance in regulatory context
- ❑ International collaboration
- ❑ Communication

must fit the criteria of promoting collaboration and dialogue on the scientific and regulatory needs for the application and acceptance of NAMs in clear regulatory context;
include international collaborative case studies on topics of interest to multiple regulatory agencies;
have largely been communicated through presentations at professional meetings and publications.

Successes



- Growing international participation
- Ongoing engagement and collaboration in our virtual world
- Emerging linkages with advances under the OECD ie AOP programme, IATA, OHTs, nanoparticles, chemical categories, read across
- Manuscripts for 2020-2021 – published and in preparation
- Examples of practical implementation – CMP BER Science Approach Document, development and updating of guidance
- Beginning to have a better understanding where current approaches and assays may not be suitable and developing solutions to address shortcomings
- Ongoing communication and outreach
- **Four** new case study proposals presented in August 2020

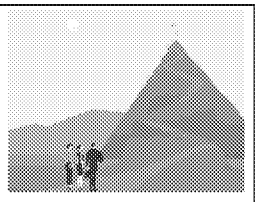
Reflections

- Progress to date clearly demonstrates value in bringing together regulatory scientists from throughout the world
- Results promise to have direct impact on use of NAM in chemical regulation internationally
- Unique role as an idea incubator or "think tank"
- Balance nature of the intergovernmental meetings with transparency and openness to larger scientific and stakeholder communities to promote broader appreciation and acceptance for application of NAMs in risk science
- Communication and knowledge transfer is an important component of the initiative

Path Forward

- APCRA will:
  - Be a platform for innovation and idea exchange between regulatory scientists
  - Lead discussions on when there is sufficient knowledge and confidence to bring NAMs into particular regulatory contexts
  - Continue to develop new collaborative case studies to address gaps in specific scientific and regulatory needs
  - Consider sharing results of the case studies through the OECD
  - Continue to communicate progress on the overall APCRA effort, using periodic public webinars and scientific publications on advances in the science

Building Confidence Through Collaboration:
Opportunities and Challenges



Challenges

- Different legislation and data requirements; requires context dependent (flexible) applications
- Confidential Data / Information
- As modern toxicity tests become increasingly prominent and scientifically robust, legislative restrictions in data requirements may limit incorporation of important information in risk assessment
- Technical expertise and new skillsets are required to apply NAMs to address a range of regulatory demands and requirements
- There is a need to communicate new and different nature of uncertainties to regulatory stakeholders
- Increasing the demonstration of regulatory relevance with use and mainstreaming implementation in current assessment contexts

Regulatory agencies are investing in the possibilities to (further) integrate New Approach Methodologies in their work, in an international collaborative approach, initiated by US EPA.

Based on global challenges for chemicals management including aggressive priority setting and assessment mandates, increasingly complex chemical landscape and many 'data poor' chemicals there is an ambition to increase the pace of assessments, and ultimately reduce animal testing.

Progress is made by conducting case studies, that trigger focussed discussions which increase the understanding of needs and potential solutions.

APCRA seen as an 'incubator' for NAM-related activities to promote collaboration and dialogue on the scientific and regulatory needs for the application and acceptance of NAMs with a clear regulatory context.
APCRA activities should complement member country participation in OECD, RCC, or various bi-lateral collaborations.
Focus on intergovernmental interactions, but continue sharing information with other stakeholders

Building Confidence Through Collaboration:

Opportunities and Challenges

Opportunities

- Capacity Building - shared resources and expertise
- Broader understanding of needs and challenges
- Increased alignment across programs and jurisdictions
- Access to data / shared (targeted) data generation to support development and validation of complex approaches for application in risk assessment activities
- Facilitates acceptance of emerging methodologies and approaches that can be valuable to regulatory decision-making
- Partnerships between risk assessment and research experts accelerate refinement and implementation of new methodologies and approaches
- Enhanced knowledge transfer and outreach across boarders and stakeholder communities
- Common goals and measures of success
- **Optimize pace, accuracy and efficiency of risk assessment**

APCRA seen as an 'incubator' for NAM-related activities to promote collaboration and dialogue on the scientific and regulatory needs for the application and acceptance of NAMs with a clear regulatory context.
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Conclusions

Regulatory agencies are investing in the possibilities to (further) integrate New Approach Methodologies in their work, in an international collaborative approach, initiated by US EPA.

Based on global challenges for chemicals management including aggressive priority setting and assessment mandates, increasingly complex chemical landscape and many 'data poor' chemicals there is an ambition to increase the pace of assessments, and ultimately reduce animal testing.

Progress is made by conducting case studies, that trigger focussed discussions which increase the understanding of needs and potential solutions.

Acknowledgments

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~THANK YOU~

"Around here, however, we don't look backwards for very long. We keep moving forward, opening up new doors and doing new things...and curiosity keeps leading us down new paths."

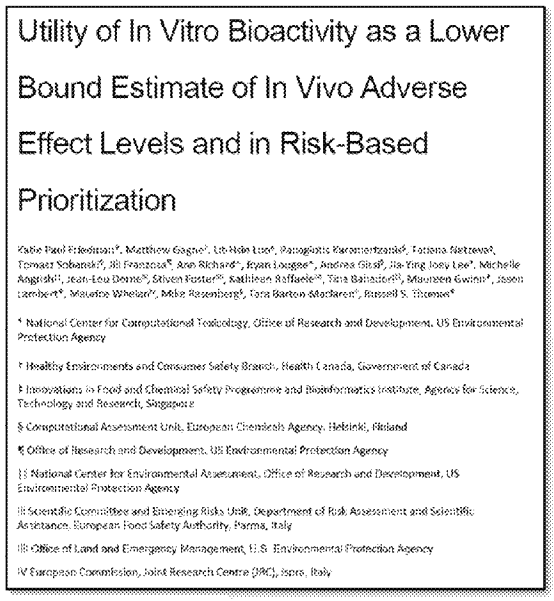
-Walt Disney

Additional Slides

Completed Case Studies

1. Retrospective Case Study Examining the Utility of In Vitro Bioactivity as a Conservative Point of Departure
   - Leads: : US EPA and Health Canada
   - Partners: EChA, EFSA, A*STAR

2. Linking Exposure to Toxicology Using Lead as Case Study
   - US EPA
   - Partners: EFSA, CalEPA, INERIS



Utility of In Vitro Bioactivity as a Lower Bound Estimate of In Vivo Adverse Effect Levels and in Risk-Based Prioritization

Katie Paul Friedman*, Matthew Gagne†, Lit-Hsin Loo‡, Panagiotis Karamertzanis§, Fotina Netzeva¶, Tomasz Sobanski||, Jill Franzosa#, Ann Richard*, Ryan Lougee**, Andrew Gissi††, Jia-Ying Joey Lee‡, Michelle Angrish‡‡, Jean-Lou Dorne§§, Steven Foster¶¶, Kathleen Raffaele¶¶, Tina Bahadori¶¶, Maureen Gwinn*, Jason Lambert*, Maurina Wheaton*, Mike Rosenberg§, Tara Barton-Maclaren†, Russell S. Thomas*

* National Center for Computational Toxicology, Office of Research and Development, US Environmental Protection Agency

† Healthy Environments and Consumer Safety Branch, Health Canada, Government of Canada

‡ Innovations in Food and Chemical Safety Programme and Bioinformatics Institute, Agency for Science, Technology and Research, Singapore

§ Computational Assessment Unit, European Chemicals Agency, Helsinki, Finland

¶ Office of Research and Development, US Environmental Protection Agency

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Scientific Committee and Emerging Risks Unit, Department of Risk Assessment and Scientific Assistance, European Food Safety Authority, Parma, Italy

** Office of Land and Emergency Management, U.S. Environmental Protection Agency

†† European Commission, Joint Research Centre (JRC), Ispra, Italy

Toxicol Sci. 2019 doi: 10.1093/toxsci/kfz201

Ongoing APCRA Case Studies

1. Prospective Case Study to assess chemicals, using and developing New Approach Methodologies (NAM) –ECHA
2. Use of transcription profiles and primary human liver cells grown as spheroids to address potency and additivity of perfluorinated alkylated substances: Applications for read-across and additivity in risk assessment of emerging PFAS –Health Canada
3. Revisiting and updating chemical categorizations with new approach methods (NAMs) – US EPA
4. Evaluation of Quantitative Structure Use Relationship (QSUR) Models with Industry-Reported Data –US EPA
5. Further Exploration of High-Throughput and Traditional Exposure Estimates to Advance NAM and Prioritization Tools for Exposure – Health Canada
6. EDC-NAM Categorization – INERIS
7. Investigating the applicability of bioactivity data to inform quantitative hazard assessments for ecological species using bioactivity-to-exposure ratios (eco-BER) – Environment Climate Change Canada
8. Substantiating Chemical Categories with Omics-derived Mechanistic Evidence (SuCCess) –ECHA
9. Evaluation of the zebrafish (Brachydanio rerio) model as an in vivo NAM that serves as an alternative to rodent assays for validating in vitro assays in the assessment of chemicals for general toxicity and endocrine disruption – Health Canada

New APCRA Case Studies

1. In vitro assessment of digestibility and gastrointestinal absorption of nanofibers –European Food Safety Authority

2. Investigating the applicability of high throughput transcriptomics data to inform quantitative hazard assessments for ecological species using bioactivity-to-exposure ratios (eco-BER) – US EPA

3. A NAM-Based Integrated Approach for Screening Potential Genotoxic Chemicals – Health Canada

4. Advanced Threshold of Toxicological Concern (TTC) for priority setting –NICNAS

New APCRA Case Study Proposals

1. Estrogen Receptor Testing with Multiple In Vitro Assays (US EPA)

2. High Throughput Toxicokinetics for In Vitro-In Vivo Extrapolation (US EPA)

3. *Benchmark Concentration Analysis in Human Bronchial Epithelial Cell Exposure to Volatile Chemicals (US EPA; tentative)*

4. *NAM development for systemic/reproductive toxicity (ECHA, tentative)*